UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/684,601	10/06/00	SMITH T	252/248

022249
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HM22/0420

EXAMINER	
ROARK, J	
ART UNIT	**PAPER NUMBER**
1644	4

DATE MAILED: 04/20/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/684,601	SMITH, TERRY	
	Examiner	Art Unit	
	Jessica H. Roark	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *1-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Applicant's amendment, filed 2/20/01 (Paper No. 3), is acknowledged.
Claims 13 and 14 have been amended.
Claims 1-19 *are pending.*

2. Applicant's election without traverse of Group II, claims 13-19 in Paper No. 3 is acknowledged.

Applicant's election with traverse of a species of IL-16 in Paper No. 3 is also acknowledged. The traversal is on the grounds that the species of IL-16 and RANTES do not yield multiplicity of invention because the instant claims recite a single compound, IgG, used to induce both IL-16 and RANTES.

Applicant's arguments with respect to the species election in the instant claims is found convincing. The species requirement between IL-16 and RANTES for Group II is withdrawn.

Claims 1-12 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 13-19 *are under consideration in the instant application.*

3. The Abstract of the Disclosure is objected to because it does not adequately describe *the claimed invention*. Correction is required. See MPEP 608.01(b).

In addition, Applicant should avoid the use of "novel" in the Abstract, as patents are presumed to be novel and unobvious.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

In addition, Applicant should avoid the use of "novel" in the title, as patents are presumed to be novel and unobvious.

5. Formal drawings have been submitted which fail to comply with 37 CFR 1.84.
Please see the enclosed form PTO-948.

6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

7. Claim 17 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Instant claim 13 recites the limitation IL-16 or RANTES; whereas dependent claim 17 recites a combination of IL-16 and RANTES.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 13-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) The terms "TAO" and "TAO fibroblast" in claim 13 render claim 13 and dependent claims 14-19 indefinite. Neither the term "TAO" nor the term "TAO fibroblast" are defined by the claim. Therefore, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

The specification discloses (e.g., on page 1) that "TAO" is an abbreviation for "Thyroid-Associated Ophthalmopathy". It is suggested that Applicant amend the claim to recite "Thyroid-Associated Ophthalmopathy" when "TAO" is used as a noun.

The specification discloses (e.g., on page 14 at line 18) that IL-16 and RANTES are produced by "TAO orbital fibroblasts". Applicant may wish to consider substituting "orbital fibroblasts from patients with Thyroid-Associated Ophthalmopathy" for "TAO fibroblast" in order to obviate the rejection with respect to "TAO fibroblast".

B) Claims 14-17 recite "analyte". There is insufficient antecedent basis for this limitation in the claims since instant claim 13 does not recite an "analyte". It is suggested that Applicant amend claim 13 to provide proper antecedent basis.

C) Claim 19 is indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of ..." with the use of the conjunction "and" in listing the species. A conjunction is needed between "ascites," and "tissue."

D) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 13-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rotella et al. (J. Clin. Endocrinol. Metabol. 1986 62:357-367) in view of Sciaky et al. (J. Immunol. 2000 164:3806-3814).

The claims are drawn to a method of detecting thyroid-associated ophthalmopathy (TAO) in a patient.

Rotella et al. teach that IgG from patients' with TAO (also known as ophthalmopathy associated with Graves' hyperthyroidism) stimulates fibroblasts to produce collagen (see entire document, especially "Abstract" and Figures 6). Rotella et al. also teach that collagen biosynthesis is an early response of a fibroblast to a stimulus, and that the clinical changes in the orbit reflect stimulation of orbital fibroblasts (e.g., see the discussion on page 366). Rotella et al. further teach that not only is there a good correlation between the class of ophthalmopathy (i.e., the severity), and the IgG-induced change in fibroblast collagen biosynthesis, but that the IgG-mediated fibroblast stimulation is only seen in patients with ophthalmopathy (see especially "Abstract", Figures 6 and 7, and the discussion on page 366).

Rotella et al. teach an assay for IgG-mediated stimulation of fibroblasts comprising:
obtaining a biological sample from a human patient with TAO consisting of blood or ascites and isolating IgG from the sample (e.g., see "Ig preparation" on page 358); and
exposing the IgG to fibroblasts, including TAO fibroblasts, in order to stimulate the fibroblasts (e.g. Figure 6 and Discussion on page 366, next to last paragraph); and
assaying fibroblast stimulation in response to IgG exposure by measuring collagen biosynthesis(e.g., 1st column, page 364; and Figure 6).

Rotella et al. do not teach measuring fibroblast-produced IL-16 or RANTES as an indicator of IgG-mediated fibroblast stimulation.

Sciaky et al. teach that stimulated fibroblasts produce IL-16 and RANTES (see entire document, especially "Abstract"). Sciaky et al. also show that TAO fibroblast produce IL-16 and RANTES; and conclude that the production of IL-16 and RANTES by fibroblasts provides an initial signal that begins the cascade of inflammatory events culminating in the tissue remodeling found in TAO (e.g., see page 3813, especially the last paragraph). Sciaky et al. also teach that the IL-16 and RANTES can be measured by ELISA (e.g., page 3807 "ELISA analysis of IL-16 and RANTES").

Given the teachings of Rotella that stimulation of fibroblasts, including TAO fibroblast, by IgG from patients' with TAO correlates with the class of ophthalmopathy; and the observation by Sciaky et al. that stimulated fibroblasts produce IL-16 and RANTES which can initiate the inflammatory cascade culminating in the tissue remodeling observed in TAO; it would have been obvious to the ordinary artisan at the time the invention was made to detect TAO in a patient by assaying for IL-16 and/or RANTES production by TAO fibroblasts stimulated with patient IgG derived from blood, ascites, or any IgG containing sample. The ordinary artisan would have been motivated to substitute an ELISA-based assay for the collagen biosynthesis assay taught by Rotella et al. in order to provide a simple and sensitive assay for detection of TAO in a patient. In addition, the observation of Sciaky et al. that fibroblast stimulation to produce IL-16 and RANTES represents an early signal in the inflammatory cascade would have further motivated the ordinary artisan to assay for these molecules as early indicators of TAO. Based on the teachings of the references, the ordinary artisan at the time the invention was made would have had a reasonable expectation of success in producing a method of detecting TAO in a patient by the recited method. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. Claims 13-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rotella et al. (J. Clin. Endocrinol. Metabol. 1986 62:357-367), in view of Smith et al. (Am. J. Pathol. 1997 151:317-322), and in further view of Lim et al. (J. Immunol. 1996 156:2566-2570).

The claims are drawn to a method of detecting thyroid-associated ophthalmopathy (TAO) in a patient.

Rotella et al. teach that IgG from patients' with TAO (also known as ophthalmopathy associated with Graves' hyperthyroidism) stimulates fibroblasts to produce collagen (see entire document, especially "Abstract" and Figures 6). Rotella et al. also teach that collagen biosynthesis is an early response of a fibroblast to a stimulus, and that the clinical changes in the orbit reflect stimulation of orbital fibroblasts (e.g., see the discussion on page 366). Rotella et al. further teach that not only is there a good correlation between the class of ophthalmopathy (i.e., the severity), and the IgG-induced change in fibroblast collagen biosynthesis, but that the IgG-mediated fibroblast stimulation is only seen in patients with ophthalmopathy (see especially "Abstract", Figures 6 and 7, and the discussion on page 366).

Rotella et al. teach an assay for IgG-mediated stimulation of fibroblasts comprising:
obtaining a biological sample from a human patient with TAO consisting of blood or ascites and isolating IgG from the sample (e.g., see "Ig preparation" on page 358); and
exposing the IgG to fibroblasts, including TAO fibroblasts, in order to stimulate the fibroblasts (e.g. Figure 6 and Discussion on page 366, next to last paragraph); and
assaying fibroblast stimulation in response to IgG exposure by measuring collagen biosynthesis(e.g., 1st column, page 364; and Figure 6).

Rotella et al. do not teach measuring fibroblast-produced IL-16 or RANTES as an indicator of IgG-mediated fibroblast stimulation.

Smith et al. teach that stimulated fibroblast produce IL-16 (see entire document, especially page 318, 2nd column). Smith et al. also teach that RANTES is overexpressed by RelB-deficient fibroblasts after stimulation with LPS compared to wildtype fibroblasts, indirectly indicating that wildtype fibroblasts can also express RANTES (see page 321, 1st column, especially last paragraph). Smith et al. teach that the fibroblast is an important sentinel cell that regulates the initiation of inflammation, and suggest that it is the synthesis of chemokines (e.g., IL-16 and RANTES) that allows the fibroblast to recruit leukocytes (see entire document, especially Title and 1st paragraph).

Lim et al. teach that IL-16 and RANTES can each be detected in the picogram range using simple ELISA assays (see entire document, especially "ELISA" on page 2567).

Given the teachings of Rotella that stimulation of fibroblasts, including TAO fibroblast, by IgG from patients' with TAO correlates with ophthalmopathy; and the observation by Smith et al. that stimulated fibroblasts produce IL-16 and RANTES; it would have been obvious to the ordinary artisan at the time the invention was made that TAO could be detected in a patient by assaying for production of IL-16 and/or RANTES by TAO fibroblasts stimulated with patient IgG derived from blood, ascites, or any IgG containing sample. The ordinary artisan would have been motivated to substitute an ELISA-based assay for the collagen biosynthesis assay taught by Rotella et al. in order to provide a simple and sensitive assay for detection of TAO in a patient. In addition, the observation of Smith et al. that chemokine production by stimulated fibroblasts is an early inflammatory signal would have further motivated the ordinary artisan to assay for these molecules as early indicators of TAO. Based on the teachings of the references, the ordinary artisan at the time the invention was made would have had a reasonable expectation of success in producing a method of detecting TAO in a patient by the recited method. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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April 18, 2001

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